

Practitioner's Docket No. MPI98-149P1USRCE2M**09/775,803****REMARKS**

Applicants thank the Examiner for withdrawing the finality of the previous Office Action and for entering the amendments filed on April 1, 2004. In response to the Office Action mailed on June 14, 2004, Applicants have amended the Specification and Claims and provide remarks below.

Claims 1, 5, 10, 15, 21, 23, 24 and 26-30 have been amended and claims 8 and 13 have been canceled. The amendments to the claims are described below in sections responding to the Examiner's objections and rejections. No new matter has been added. Claims 1, 3, 5, 10, 15, 21, 23, 24, and 26-30 are pending. Further remarks are set forth below with reference to the sections of the Office Action.

Objections to the Specification

The Examiner objected to the lack of sequence identification numbers in the descriptions of the drawings. In response, Applicants have amended the specification to include SEQ ID NOs in the descriptions of the drawings. In view of these amendments, Applicants respectfully request that this objection be withdrawn.

The Examiner also objected to the lack of status information for a US patent application incorporated by reference. In response, Applicants have amended the specification to include status information regarding that patent application. In view of this amendment, Applicants respectfully request that this objection be withdrawn.

Objections to the Claims

The Examiner objected to claims 5 and 10 for informalities related to the contents of a nucleic acid molecule. Applicants have amended claims 5 and 10 to incorporate the Examiner's comment. The objections to claims 8 and 13 are moot due to the cancellation of these claims. In view of these amendments, Applicants respectfully request that this objection be withdrawn.

The Examiner also objected to the grammar in claim 24. Applicants have amended claim 24 according to the Examiner's suggestion. In view of this amendment, Applicants respectfully request that this objection be withdrawn.

Rejection of Claims Under 35 U.S.C. §112, First Paragraph

Claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, and 26-30 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the full scope of the invention. The Examiner argues that the scope of the claims does not enable one

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skilled in the art to produce a transgenic mouse with a phenotype described in the specification without undue experimentation. The Examiner acknowledges that the specification is enabled for a method of producing a transgenic mouse whose genome comprises a homozygous disruption in its GPV gene and wherein the transgenic mouse has a decreased bleeding time compared to a wild type mouse, but is not enabled for a mouse wherein at least one allele of the gene has been modified. Without acquiescing to the Examiner's position, but in the interest of advancing this application, Applicants have amended claims 1, 5, 10, 15, 21, 23 and 28-30 (claims 3, 24, 26 and 27 being dependent claims and claims 8 and 13 being canceled) to recite that the transgenic mouse has a homozygous modification of the GP V gene from the claimed method. Support for these amendments can be found in the Specification at, for example page 6, lines 17-18. In view of these amendments, Applicants respectfully request that this rejection be withdrawn.

The Examiner further rejects claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, and 26-30 under 35 U.S.C. §112, first paragraph, because the term "comprising" to refer to the nucleotides removed from GP V still read on the transgenic mouse produced by Kahn et al. (Blood 94:4112-4121, 1999). In this publication, Kahn et al. produced a transgenic GP V-deficient mouse and did not observe the phenotype reported by Applicants in the present application. Applicants respectfully traverse this rejection.

The Examiner acknowledges that the methods practiced by both Applicants and Kahn et al. produced -/- mice which "resulted in non-expression of the GP V gene" (page 6 of Office Action). The Examiner alleges that the art of transgenics is not predictable art with respect to modifying a gene in a mouse and reasonably predicting the resulting phenotype from the modification." The Examiner was not convinced by Applicants arguments that different methodology for studying the phenotype of the resulting transgenic mice led Kahn et al. to different conclusions than those reached by the Applicants. Applicants herewith submit Exhibits A and B to help justify retaining the "comprising" term to refer to the construct used to eliminate GP V expression in the claims.

Exhibits A and B consist of published articles wherein the laboratories of Applicants (in Exhibit A, Ramakrishnan et al.) and Kahn et al. (in Exhibit B, Moog et al.) report on further studies using their respective transgenic mice. While the overall purposes of the two articles are different (Ramakrishnan et al. decipher the signaling pathway from the GP Ib-IX-V complex and Moog et al. study the participation of GP V in collagen aggregation), the articles do include studies to reconcile the apparent phenotype differences of the earlier reports. On pages 1825-1826 and figures 3 of Exhibit A, Ramakrishnan et al. used GPV null platelets from Applicants' -/- mice to dissect the ways thrombin mediates a signaling response in platelets and dissect the methodology used by Kahn et al. to study the thrombin response by the GPV null platelets from Kahn's -/- mice. As explained on pages 1827-1828, the conditions used by Kahn et al. favored thrombin action through an alternative pathway, mediated by PARs (protease

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activated receptors). Those conditions thus rendered Kahn et al. unable to observe the increased thrombin aggregation response observed by Applicants. Furthermore, on page 1041, figure 3C of Exhibit B, Moog et al. performed thrombin aggregation assays on GPV null platelets from Kahn's -/- mice and acknowledged the increased responsiveness to a low concentration of thrombin by these platelets (see also page 1044, beginning of last paragraph). These two sets of studies clearly establish the similarities of phenotypes of the GP V -/- mice of Applicants and Kahn et al. and the fact that both Applicants and Kahn et al. produced GP V knockout mice. However, Moog et al., on page 1045 of Exhibit B, after apparent further study of the bleeding time of Kahn's -/- mice were unable to observe the shortened bleeding time observed by Applicants. Without elaborating on the methodology, Moog et al. offer that differences in the bleeding time procedures led to these different observations. As a result, Applicants have further amended claims 1, 5, 10, 15, 21, 23 and 28-30 (claims 3, 24, 26 and 27 being dependent claims and claims 8 and 13 being canceled) to recite a phenotype that the claimed transgenic mice have platelets an increased aggregation response to a low concentration of thrombin. Support for these amendments can be found in the Specification, for example at page 8 line 17 and page 23, lines 7-10. These amendments result in claims which now recite a phenotype whose methodology depends on confirmed established technology and is replicable regardless of the method for producing the transgenic mice. In view of these amendments and remarks, Applicants respectfully ask that this rejection be withdrawn.

Rejection of Claims Under 35 U.S.C. §112, Second Paragraph

Claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, and 26-30 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner rejected these claims for reading on heterozygous GP V +/- mice when reciting decreased bleeding time. Applicants respectfully traverse this rejection.

Applicants have amended claims 1, 5, 10, 15, 21, 23 and 28-30 (claims 3, 24, 26 and 27 being dependent claims and claims 8 and 13 being canceled) to recite the transgenic mouse has a homozygous modification of the GP V gene from the claimed method. The claims no longer read on heterozygous GP V +/- mice. In view of these amendments, Applicants request that this rejection be withdrawn.

The Examiner further rejected claims 5 and 10 under 35 U.S.C. §112, second paragraph, for the omission of essential active steps for determining the phenotype of decreased bleeding time of the transgenic mouse. The Examiner states that the claim does not define active steps if the bleeding time of the transgenic mouse is not less than the bleeding time of a mouse homozygous for the GPV gene (emphasis added) (i.e. this additional bleeding time step would signify a mouse which does not have the claimed homozygous modification). Applicants respectfully traverse this rejection. The methods for claims 5 and 10 are methods for producing a transgenic mouse homozygous for removal of GP V gene,

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not methods for determining a bleeding time phenotype. Applicants have amended the claims so the methods result in a homozygous transgenic GP V $-/-$ mouse. The homozygous genotype determines the observed phenotype. The specification describes methods in studying the claimed phenotype. Applicants also note that phenotype determination steps are not necessarily required to be detailed on claims for methods to produce transgenic mice, even if a phenotype is recited in the preamble or in the body of the claim (see e.g., US Patent Numbers 6,784,335, 6,765,126, 6,750,375 or 6,740,793). Therefore, Applicants are confused by this attempt by the Examiner to add steps to the claimed method in the present application. In view of these remarks, Applicants respectfully request that the Examiner withdraw this rejection. If the Examiner disagrees with these remarks, Applicants request that the Examiner offer further guidance by way of a phone call or another Office Action.

The Examiner further rejected claims 5, 8, 10 and 13 under 35 U.S.C. §112, second paragraph, because the sequence of the construct in the preamble is not also defined by the claim. Claims 8 and 13 have been canceled. Claims 5 and 10 have been amended so step a) of each claim recite the sequence removed by the method. In view of these amendments, Applicants request that this rejection be withdrawn.

Claim 13 was further rejected under 35 U.S.C. §112, second paragraph, because of an alleged omitted element. Specifically, the omitted element is the definition of the type of chimeric mouse used in step f). While claim 13 is canceled, this step is analogous to the new step f) in claim 10. New step f) in claim 10 defines the mouse used in the crossing step. In view of this amendment, Applicants request that this rejection be withdrawn.

Claims 24 and 26 were rejected under 35 U.S.C. §112, second paragraph, for having omitted steps. Applicants have amended claim 24 to depend from claim 5 and have amended claim 26 to depend from claim 1. In view of these amendments, Applicants request that this rejection be withdrawn.

Claims 26 and 27 were rejected under 35 U.S.C. §112, second paragraph, for having insufficient antecedent basis. Applicants have amended claims 26 and 27 to depend from claim 1. In view of this amendment, Applicants request that this rejection be withdrawn.

CONCLUSIONS

The foregoing amendments and remarks are being made to place the Application in condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims. Applicants respectfully submit that the rejections of claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, and 26-30 under 35 U.S.C. §112 are herein overcome and that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned.

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This paper is being filed timely as a request for a one month extension is being filed concurrently herewith. No additional extensions of time are required. If additional extensions of time are required, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

October 14, 2004

Respectfully submitted,

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